



The Value of Exercise Training for Prevention and Complementary Treatment of Brain Aging and Neurodegeneration

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It is widely documented that sedentarism is a risk factor for most common age-related chronic diseases. Regarding brain's health, there is increasing evidence of the beneficial effects of aerobic physical exercise on synapse and general brain function, at both young and old ages and in both healthy and pathological states [1]. Indeed, in adult animals, physical training has been shown to enhance performance in learning and memory tasks [2-4], increase neuronal proliferation [5-7], and affect neuronal structure and the functionality of cellular mechanisms associated with learning processes [8,9]. In addition, several studies using transgenic mouse models of Alzheimer's disease (AD) have demonstrated the protective effects of aerobic exercise against neurodegeneration [10,11].

Although transcriptional responsiveness varies over the lifetime, many brain genes still seem to be responsive to exercise in old animals and in animal models for neurodegenerative diseases [12-14]. In mice, brain gene expression is sensitive to physical exercise, particularly in the hippocampus [15-19]. These findings are particularly relevant because the hippocampus is especially susceptible to dysfunctional and degenerative processes during aging or in Alzheimer's disease, plays a key role in learning and memory processes and is involved in the regulation of mood and antidepressant responses [20-22]. Using the senescence-accelerated SAMP8 mouse a non-transgenic model for studying aspects of progressive cognitive decline and Alzheimer's disease (AD) we have recently shown that exercise training during adulthood (6 months of voluntary training on a running wheel, 3 alternate days per week) prevented or delayed processes associated with aging [23]. Upon completion of the long-term intervention, SAMP8 mice were at the final stage of their lives (their median life is 9.7 months [24]), however they were still voluntarily running and showed improvement in several aging traits compared with the sedentary controls. We found that the exercise intervention ameliorated their skin color, decreased body tremor, increased hippocampal vascularization and modulated the expression of the brain derived neurotrophic factor (*Bdnf*) gene as well as several extracellular matrix gene alterations in the hippocampus. Recent data have described that epigenetic modifications seem to be involved in the peripheral and central effects of physical exercise [25]. Notably, we have recently observed epigenetic changes in specific microRNA (miRNA) and histone acetylation levels in the hippocampus of senescent SAMP8 mice in response to 8 weeks of voluntary wheel running (Cosin-Tomas et al., unpublished data).

In sum, there is a growing body of research showing the neurophysiological aging-protective responses elicited by exercise training. Moreover, a still limited but fascinating field has begun to describe the epigenetic impact of physical exercise in peripheral tissues and in the brain. Unveiling the exercise-responsive mechanisms of chromatin regulation and their pathophysiological implications may lead to the development of new preventive and/or therapeutic interventions for age-related disorders, including neurodegenerative conditions.

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Received December 23, 2013; Accepted January 23, 2014; Published January 27, 2014

Citation: Kaliman P (2014) The Value of Exercise Training for Prevention and Complementary Treatment of Brain Aging and Neurodegeneration. *J Yoga Phys Ther* 4: 152. doi:10.4172/2157-7595.1000152

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Citation: Kaliman P (2014) The Value of Exercise Training for Prevention and Complementary Treatment of Brain Aging and Neurodegeneration. J Yoga Phys Ther 4: 152. doi:[10.4172/2157-7595.1000152](https://doi.org/10.4172/2157-7595.1000152)

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